Improving the long-term prognosis of anxiety disorders

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CHAPTER 5

Risk of relapse after antidepressant discontinuation in anxiety disorders, obsessive-compulsive disorder, and post-traumatic stress disorder: systematic review and meta-analysis of relapse prevention trials

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Abstract

Objectives: To examine the risk of relapse and time to relapse after discontinuation of antidepressants in patients with anxiety disorder who responded to antidepressants, and to explore whether relapse risk is related to type of anxiety disorder, type of antidepressant, mode of discontinuation, duration of treatment and follow-up, comorbidity, and allowance of psychotherapy.

Design: Systematic review and meta-analyses of relapse prevention trials.

Data sources: PubMed, Cochrane, Embase, and clinical trial registers (from inception to July 2016).

Study selection: Eligible studies included patients with anxiety disorder who responded to antidepressants, randomised patients' double blind to either continuing antidepressants or switching to placebo, and compared relapse rates or time to relapse.

Data extraction: Two independent raters selected studies and extracted data. Random effect models were used to estimate odds ratios for relapse, hazard ratios for time to relapse, and relapse prevalence per group. The effect of various categorical and continuous variables was explored with subgroup analyses and meta-regression analyses respectively. Bias was assessed using the Cochrane tool.

Results: The meta-analysis included 28 studies (n=5233) examining relapse with a maximum follow-up of one year. Across studies, risk of bias was considered low. Discontinuation increased the odds of relapse compared with continuing antidepressants (summary odds ratio 3.11, 95% confidence interval [CI95%] 2.48 to 3.89). Subgroup analyses and meta-regression analyses showed no statistical significance. Time to relapse (n=3002) was shorter when antidepressants were discontinued (summary hazard ratio 3.63, CI95% 2.58 to 5.10; n=11 studies). Summary relapse prevalences were 36.4% (CI95% 30.8 to 42.1%; n=28 studies) for the placebo group and 16.4% (CI95% 12.6 to 20.1%; n=28 studies) for the antidepressant group, but prevalence varied considerably across studies, most likely owing to differences in the length of follow-up. Dropout was higher in the placebo group (summary odds ratio 1.31, CI95% 1.06 to 1.63; n=27 studies).

Conclusions: Up to one year of follow-up, discontinuation of antidepressant treatment results in higher relapse rates among responders compared with treatment continuation. The lack of evidence after a one year period should not be interpreted as explicit advice to discontinue antidepressants after one year. Given the chronicity of anxiety disorders, treatment should be directed by long-term considerations, including relapse prevalence, side effects, and patients' preferences.

Introduction

In anxiety disorders, chronic course trajectories and relapses after remission are common (1–6). Consequently, when combined with high prevalence rates and functional limitations (7,8), anxiety disorders score highly on burden of disease rankings (9–12). Optimising the long-term prognosis, including prevention of relapse (13), is an important strategy to decrease the burden of disease related to anxiety.

In addition to cognitive behavioural therapy, antidepressants are a first line option for the treatment of anxiety disorders (14,15), as they are effective and generally well tolerated (16,17). Most (57%) patients with anxiety disorders who are being treated use drugs (18). As long-term studies are scarce, whether antidepressants should also be regarded a first line treatment option for optimising long-term prognosis remains largely unknown. International guidelines are therefore consensus-based and advise continuation of treatment for variable durations (six to 24 months) and subsequent tapering of the antidepressant (18). In contrast to the guidelines' advice, long-term use is increasing, with nearly half of patients in the UK and approximately two thirds of those in the USA continuing antidepressants for at least two years (19–21). Whether clinicians are unnecessarily medicalising their patients or whether guidelines are too optimistic by advising discontinuation of antidepressants after sustained remission remains unclear. This discrepancy calls for clarity regarding long-term use of antidepressants: is discontinuation of antidepressants wise?

A previous meta-analysis, including studies up to 2008, reported that relapse occurred in 26 to 45% of patients with anxiety disorder who discontinued antidepressants (22). Continuing antidepressants seemed to be effective in preventing relapse, with protective summary odds ratios ranging from 0.20 to 0.38 in various anxiety disorders (22). Superiority of antidepressants to placebo was also shown for quality of life (23).
Information on whether specific treatment or discontinuation strategies influence risk of relapse is scant and inconclusive. For example, whereas some studies reported fewer relapses when antidepressants were discontinued after sustained use (24,25), others reported that relapses occurred frequently when antidepressants were stopped after a prolonged period of use (26–28). Likewise, we do not know whether risk of relapse depends on the type of antidepressant, the mode of discontinuation (abrupt versus tapered), the duration of follow-up, and whether concomitant psychotherapy is allowed or whether comorbidity affects relapse risk after discontinuation of antidepressants.

With this meta-analysis, we aimed to verify, update, and extend current knowledge. We meta-analysed relapse prevention trials that included patients with anxiety disorder, obsessive-compulsive disorder, or post-traumatic stress disorder who responded to antidepressants, randomised these patients in a double blind fashion to either continuing the antidepressant or switching to placebo, assessed the prevalence of relapse per treatment group, and compared the risk of relapse or time to relapse between these groups. Additionally, we explored whether this relapse risk is related to the type of

anxiety disorder, type of antidepressant, mode of discontinuation, duration of previous treatment, duration of follow-up, whether studies allowed concurrent psychotherapy, whether studies excluded comorbidity, and involvement of drug companies. Finally, we briefly report on tolerability, given the importance for daily clinical practice.

Methods

Literature search

We searched PubMed, Cochrane, and Embase (from inception to July 2016) for studies including patients with anxiety disorder who responded to antidepressants, which subsequently randomised patients to either continuing the antidepressant or switching to placebo and compared (time to) relapse between these groups. A librarian and NMB did the search by using (combinations of) free text and keywords indicating anxiety disorders, antidepressants, discontinuation, and randomised controlled trials (Appendix 5.1 gives the search terms used). Language was unrestricted. This search was extended by scanning reference lists of relevant papers and searching trial registers including Clinicaltrials.gov, World Health Organization, Cochrane trials, GlaxoSmithKline, Roche, Novartis, and AstraZeneca.

Study selection criteria consisted of the following. 1) Studies focused on patients with panic disorder, agoraphobia, social phobia, generalised anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, or specific phobia; comorbidity was allowed. 2) Patients were classified as responders after treatment with antidepressants; studies focusing on drug treatment while allowing concomitant psychotherapy were included. 3) A double blind, placebo controlled design was used, randomising patients to long-term use of antidepressants (antidepressant group) or switching to placebo (placebo group). 4) Relapse and/or time to relapse were assessed after a follow-up period. 5) Articles not presenting original data or consisting of only abstracts were excluded. We used the definitions of response and relapse as used in the original studies.

Two independent raters (NMB and WDS) assessed titles and abstracts for eligibility. Two independent raters (NMB and RCB) then assessed the method sections of the selected articles and resolved disagreements through discussion. This method section was reported in accordance with the PRISMA guidelines (29).

Data extraction

From each study, NMB and RCB independently extracted the following aspects for the active treatment phase: the anxiety disorder, inclusion and exclusion criteria, type and dosage of antidepressant, sample size, duration of treatment, definition of response, and proportion of responders. For the follow-up phase, we extracted sample size, age, duration of follow-up, definition of relapse, proportion of and time to relapse per treatment arm, corresponding statistics, mode of discontinuation (tapering versus abrupt),

dropouts, tolerability, and withdrawal symptoms. Discrepancies were resolved by referral to the data of the original article. For each study, the odds ratio, indicating the odds of relapse in the placebo group relative to the odds of relapse in the antidepressant group, was based on the number of relapses per group and the total number of patients per group. We also used this information to calculate the corresponding confidence intervals and the prevalence of relapse per treatment group. For time to relapse, we used the hazard ratio and its corresponding confidence interval as reported by the individual studies. If not reported, estimations of the 95% confidence interval were based on methods described by Parmar and colleagues and Tierney and colleagues (30,31).

Quality assessment and publication bias

To assess the quality of the studies, KMH and RCB scored studies independently by using the Cochrane tool for assessing risk of bias (32). Studies were scored 'low risk', 'high risk', or 'unclear' on the domains random sequence generation and allocation concealment (selection bias), blinding of patients and providers (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias) (Appendix 5.2). Because the blinding of patients may be breached by the experience of withdrawal symptoms, we considered the risk of bias to be high when antidepressants were discontinued abruptly, unless it was reported that adverse events after randomisation did not differ between groups. We considered attrition bias to be high when 15% or more of the total number of patients dropped out during follow-up. Consensus on the ratings was reached through discussion. We summed the number of items scoring 'high' to obtain a summary score, which could range from 0 to 7, with low scores indicating a low risk of bias. The summary score was included in a meta-regression analysis as the variable 'quality'.

To assess publication bias, we created funnel plots and used Duval and Tweedie's trim and fill procedure provide an adjusted estimate of the odds ratios and hazard ratios (33). Importantly, funnel plot asymmetry can result from (a combination of) publication or other selection biases and poor methodological quality in small studies, but it may also be due to true heterogeneity, artefacts, and chance (34,35). Additionally, as the Duval and Tweedie trim and fill method relies on the assumption that publication bias is the only reason for funnel plot asymmetry (34), results should be interpreted with caution.

Meta-analysis

We did a random effects meta-analysis (DerSimonian-Laird method (36)) to summarise the difference in 'proportion of relapse' between antidepressants and placebo. We used odds ratios and corresponding 95% confidence intervals to summarise data. Additionally, as the event under study (relapse) may be fairly common, the odds ratio may overestimate the risk ratio. To avoid overestimating results, we also used the risk ratio and its corresponding 95% confidence interval to summarise data. Although the DerSimonian-Laird method is widely used, this method tends to provide confidence intervals that are

too narrow, resulting in inappropriate numbers of type I errors. To overcome this, reported confidence intervals are adjusted by means of the Hartung-Knapp-Sidik-Jonkman method (37–39). P-values for the random effects subgroup analyses are based on the Q test for heterogeneity using the Hartung-Knapp-Sidik-Jonkman adjusted variance per subgroup (37–40). Meta-analysis was based on intention to treat samples or, if they were not available (41,42), on responder samples.

We defined subgroup analyses a priori and did them for the following categorical variables: type of anxiety disorder according to the 'Diagnostic and Statistical Manual of Mental Disorders', fourth edition (DSM-IV generalised anxiety disorder, social phobia, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder), with a separate analysis for anxiety disorders according to DSM-5 (which excludes obsessive-compulsive disorder and post-traumatic stress disorder); type of antidepressant (selective serotonin reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor, other); mode of discontinuation (abrupt, taper or fluoxetine (which tapers by itself)); concurrent psychotherapy allowed (no/yes); whether (most) comorbidity was excluded (no/yes); and involvement of drug companies. We used meta-regression analysis to estimate the influence of the year of publication, the quality of individual studies, the duration of treatment, and the duration of follow-up on the outcomes of studies.

In a separate random effects meta-analysis, we examined the 'time to relapse'. We used hazard ratios and corresponding 95% confidence intervals to summarise these data, with hazard ratios reflecting the hazard rate of time to relapse in the placebo group divided by the hazard rate of time to relapse in the antidepressant group.

In addition to the meta-analyses for the relative treatment effects (odds ratio of relapse, hazard ratio of time to relapse), we calculated summary prevalence of relapse per treatment group (antidepressant group, placebo group) and summary prevalence of dropout per treatment group (antidepressant group, placebo group) and the corresponding 95% confidence intervals by using random effects meta-analyses. The summary relapse prevalence per treatment group is of more direct relevance to clinicians and patients for making informed treatment decisions, although its generalisability may be more limited than that of relative effect measures (43). The summary relapse summarises the number of participants relapsing per treatment group relative to the total number of participants in that group. Prevalences per treatment group were weighted for group sample size of the individual studies. The summary dropout prevalences per treatment group were created in analogue to the summary relapse prevalences per treatment group.

We used random effect models for the meta-analyses because we expected heterogeneity across studies. The Q statistic and I^2 were reported as measures for heterogeneity between studies. I^2 reflects observed heterogeneity in percentages, with 0% indicating no heterogeneity and 25%, 50%, and 75% considered to be low, medium, and high levels of heterogeneity (44). We used RevMan to produce forest plots to visualise summary odds ratios, summary hazard ratios, and their corresponding confidence intervals (45). We used the software package Comprehensive Meta Analysis, version 3.3.070, for analyses (46).

Patient involvement

The Dutch patient association for anxiety disorders (angst, dwang en fobiestichting: www.adfstichting.nl) often receives questions about medication policies after the acute phase, and therefore welcomes this meta-analysis. The association will inform patients about the results. Because this study is a meta-analysis, no patients were involved in the design. No patient involvement was reported in the original studies.

Results

The literature search resulted in 2934 records. Of these, we assessed 50 full text articles for eligibility and included 24 (Figure 5.1). Six unpublished studies were identified by hand searching and by searching clinical trials registers. Of these, two could not be included owing to missing data, as data were not provided on request. One of the articles with missing data concerned a study with a non-significant trend favouring continuation treatment (47,48); the other is registered on clinicaltrials.gov (49), but the results are not described. We included the remaining four unpublished studies (50-53) all conducted by GlaxoSmithKline. This resulted in a total of 28 studies meeting inclusion criteria for proportion of relapse (24,41,42,48,50–73). Eleven of these also reported on time to relapse (24,54–58,60,68,70,72,73). Data about the corresponding 95% confidence interval of the hazard ratios was unavailable for two studies and not provided by the authors on request (24,54), so we based estimations of the 95% confidence intervals on methods described elsewhere (30,31).

Characteristics of studies

The 28 included studies examining relapse were published between 1995 and 2012 (Appendix 5.3). Sample sizes of the relapse prevention phase ranged from 15 to 561, resulting in n=2625 patients in the antidepressant group and n=2608 in the placebo group (total n=5233). Six studies focused on panic disorder, five on social phobia, six on generalised anxiety disorder, seven on obsessive-compulsive disorder, and four on post-traumatic stress disorder. The duration of treatment ranged from eight to 52 weeks, as did the duration of follow-up. Two studies had a variable duration of follow-up of 24 to 76 week and 24 to 56 weeks (55,56). Because all patients in these two studies had an assessment at 24 weeks, we used data at 24 weeks as the outcome for these studies. The second meta-analysis examining time to relapse was based on 11 studies with n=1511 patients in the antidepressant group and n=1491 patients in the placebo group (total n=3002). The duration of follow-up ranged from 24 to 28 weeks. One study had a variable duration of follow-up of 24 to 56 weeks (56). We assessed bias in all studies by using the Cochrane tool (32). Performance bias related to blinding of providers and detection bias was rated low in all studies. By contrast, attrition bias was present in most studies. Across studies, the summary score ranged from 0 to 3, with two studies scoring 0, 14 studies

scoring 1, 10 studies scoring 2, and two studies scoring 3 (see Appendix 5.2). Thus, the risk of bias was generally low.

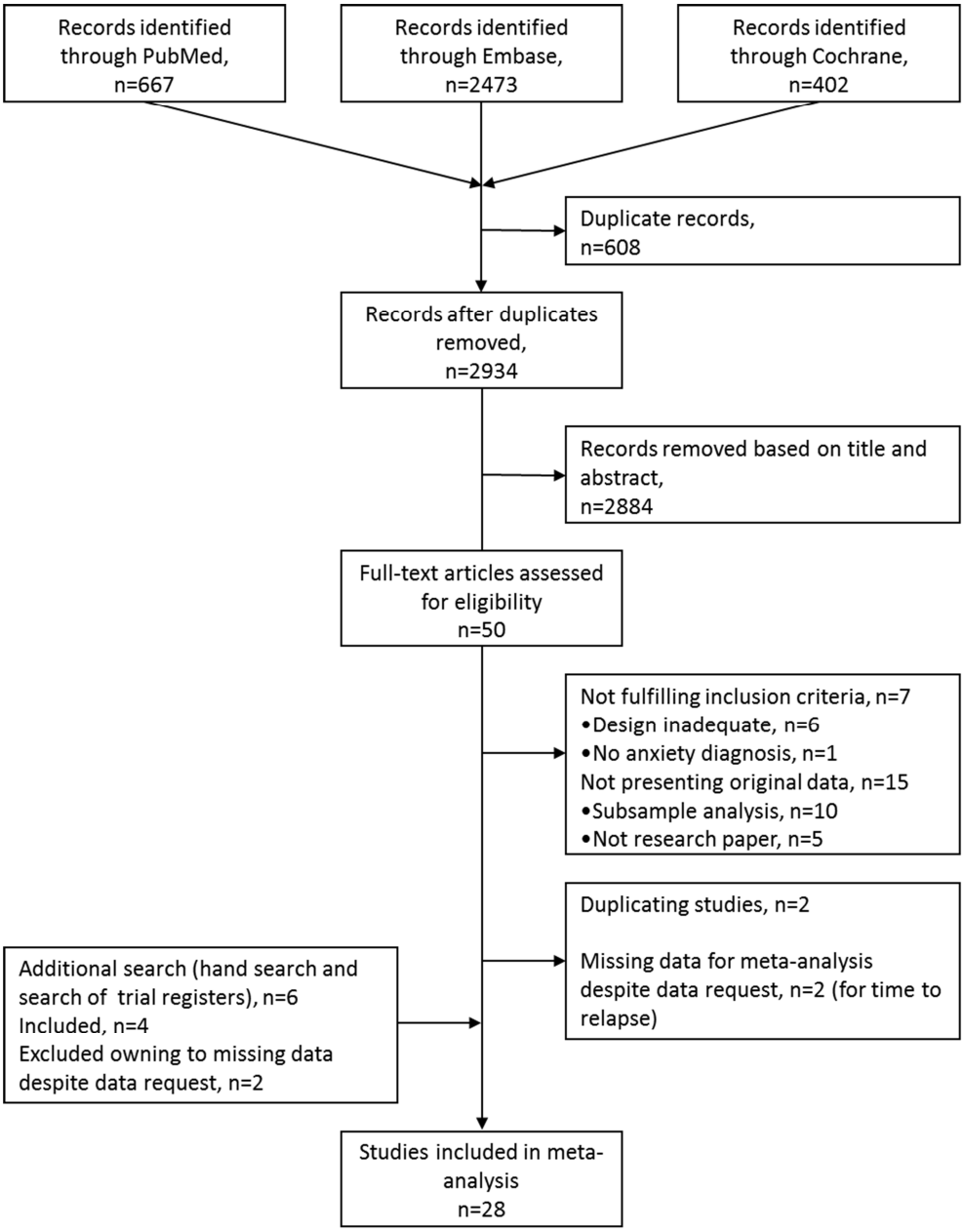

Figure 5.1: Flow chart of literature search.

Proportion of relapse

The summary odds ratio of relapse was 3.11 (95% confidence interval [CI95%] 2.48 to 3.89; n=28 studies) for patients in the placebo group relative to patients in the antidepressant group (Table 5.1; Figure 5.2), indicating that more patients relapsed after discontinuation of antidepressants than when antidepressants were continued for studies with a duration of follow-up ranging between eight and 52 weeks. The Q statistics provided no indications of significant dispersion across studies (Q=29.37, df=27, p=.34). Based on I^2, 8.07% of the total variance was related to true heterogeneity between studies. Inspection of the funnel plot (Appendix 5.4) seems to show some asymmetry, which could indicate small study effects. The Duval and Tweedie trim and fill procedure suggested little change in the odds ratio after adjustment (summary adjusted odds ratio 2.98, CI95% 2.39 to 3.72; n=28 studies). The summary risk ratio was 2.21 (CI95% 1.85 to 2.64; n=28 studies), indicating that the odds ratio overestimates the risk ratio for relapse.

Subgroup analyses and meta-regression analyses

We did several exploratory subgroup analyses (Table 5.1). In line with the indications of limited heterogeneity across studies by Q and I^2, type of anxiety disorder, type of antidepressant, mode of discontinuation, allowing concurrent psychotherapy, and exclusion of comorbidity did not statistically affect the odds ratio of relapse. Likewise, outcomes seemed statistically unrelated to year of publication (p=.25), quality of the studies based on Cochrane tool for assessing risk of bias (p=.44) (32), duration of treatment (p=.95), or duration of follow-up (p=.24). Although planned, we did not do a subgroup analysis on the involvement of drug companies, as these were involved in all but two small studies (64,71).

Time to relapse

Analysis showed that discontinuation of antidepressant resulted in a shorter time to relapse in the placebo group than in the antidepressant group (summary hazard ratio 3.63, CI95% 2.58 to 5.10; n=11 studies) (Figure 5.3). The hazard ratio reflects the total follow-up period, ranging from 24 to 28 weeks with one study having a variable duration of 24 to 56 weeks (56). The Q statistic provided no indications of significant dispersion across studies (Q=9.85, df=10, p=.45). Furthermore, I^2 is 0% as the number of degrees of freedom is higher than the value of Q. Owing to the limited number of studies, we did no subgroup analyses or meta-regression analyses. On the basis of the funnel plot, few small study effects were present, although the limited number of studies precludes a firm conclusion (Appendix 5.5).

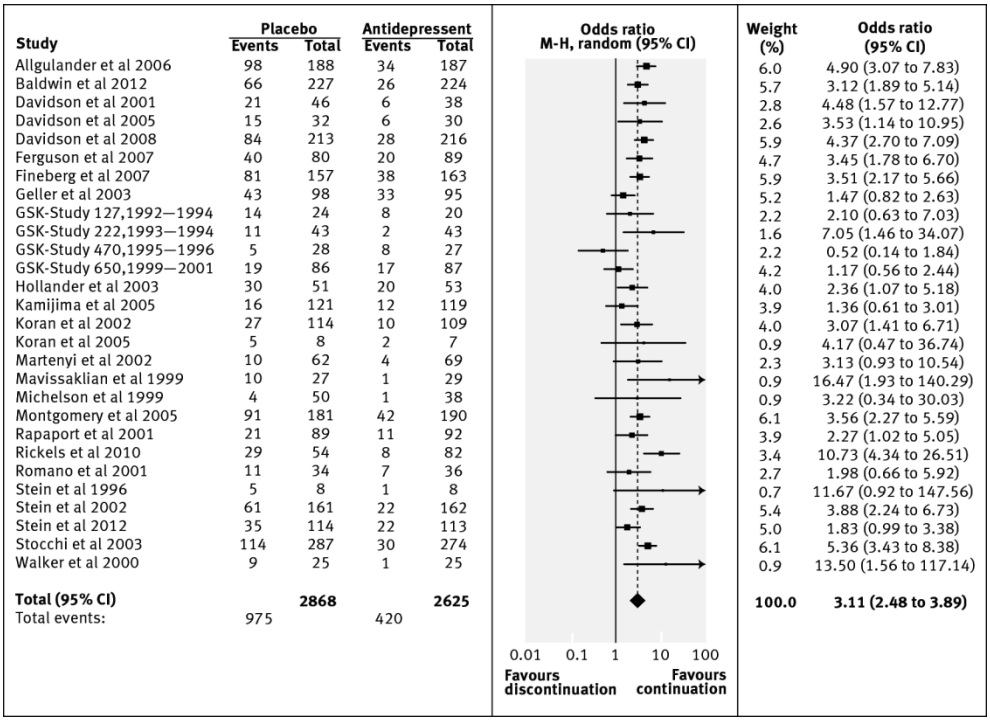

Figure 5.2: Forest plot representing odds ratios of relapse per study.

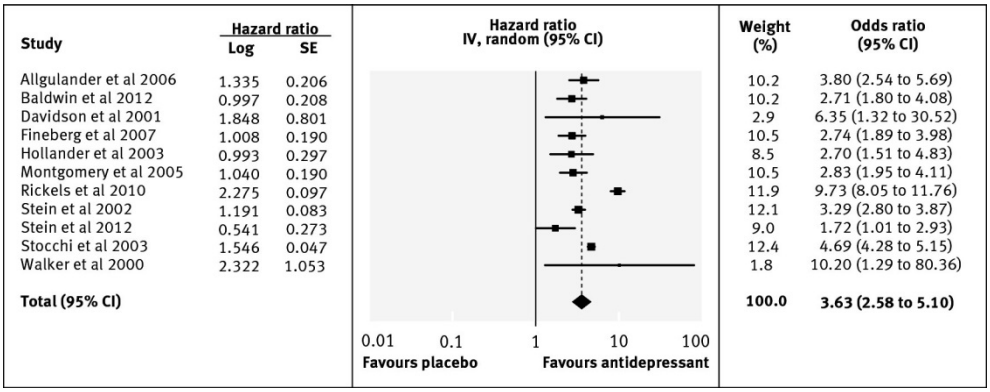

Figure 5.3: Forest plot representing hazard ratios of time to relapse per study.

Table 5.1: Results of mixed effect meta-analysis and mixed effect subgroup analyses of studies on relapse after discontinuation of antidepressants in anxiety disorders.

Meta-analysis/subgroup analysis	References	No of studies	Odds ratio (95% CI)*	Q	I^2	DF (Q)	P
Relapse		28	3.11 (2.48 to 3.89)	29.37	8.07	27	
Anxiety DSM-IV:		28	3.03 (2.44 to 3.78)	30.24	10.73	4	0.29
Generalised anxiety disorder	(24,48,54–57)	6	4.20 (2.42 to 7.28)	6.26	20.11	5	
Obsessive-compulsive disorder	(50,58–63)	7	2.43 (1.74 to 3.38)	2.32	0	6	
Panic disorder	(42,51,64–67)	6	2.88 (1.37 to 6.03)	5.47	8.59	5	
Post-traumatic stress disorder	(41,53,68,69)	4	2.45 (0.86 to 6.97)	3.21	6.50	3	
Social phobia	(52,70–73)	5	3.19 (1.02 to 9.95)	8.61	53.56	4	
Anxiety DSM-5:		17	3.55 (2.53 to 4.98)	19.92	19.67	2	0.58
Generalised anxiety disorder	(24,48,54–57)	6	4.21 (2.40 to 7.37)	5.45	8.19	5	
Panic disorder	4(42,51,64–67)	6	2.92 (1.37 to 6.22)	5.10	1.96	5	
Social phobia	(52,70–73)	5	3.17 (0.97 to 10.40)	8.12	50.74	4	
Antidepressant:		28	3.33 (2.65 to 4.17)	29.14	7.34	2	0.25
SSRI	(41,42,50–55,58–61,63,66–73)	21	2.86 (2.17 to 3.78)	20.73	3.54	20	
SNRI	(24,48,65)	3	5.03 (1.31 to 19.40)	2.19	8.62	2	
Other	(56,57,62,64)	4	2.92 (1.03 to 8.23)	3.20	6.14	3	
Discontinuation:		28	3.05 (2.44 to 3.81)	32.16	16.03	1	0.10
Abrupt	(50,51,56,57,59,60,66–68,70,73)	11	2.52 (1.80 to 3.52)	8.60	0	10	
Taper	(24,41,42,48,52–55,58,61–65,69,71,72)	17	3.61 (2.60 to 5.02)	20.69	22.66	16	
Concurrent psychotherapy allowed:		28	3.17 (2.54 to 3.95)	32.44	16.78	1	0.10
No	(50,53,56–63,65,68–70,73)	15	2.64 (2.06 to 3.37)	9.69	0	14	
Yes	(24,41,42,48,51,52,54,55,64,66,67,71,72)	13	3.86 (2.49 to 5.98)	19.45	38.30	12	
Comorbidity mostly excluded:		28	3.11 (2.45 to 3.93)	29.87	9.62	1	0.62
No	(41,42,59,60,63,64,66,68,71,73)	10	2.82 (1.74 to 4.57)	8.21	0	9	
Yes	(24,48,50–58,61,62,65,67,69,70,72)	18	3.20 (2.37 to 4.32)	21.42	20.63	17	

DSM=Diagnostic and Statistical Manual of Mental Disorders; SNRI=serotonin-noradrenalin reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor. *All confidence intervals are Hartung-Knapp-Sidik-Jonkman adjusted.

Relapse prevalence per treatment group

In addition to the meta-analyses for the relative treatment effects (odds ratio of relapse, hazard ratio of time to relapse), we calculated summary relapse prevalences per treatment group. The summary relapse prevalences per treatment group are based on studies (n=28) with follow-up duration ranging from eight to 52 weeks. The summary relapse prevalence in the antidepressant group indicated that 16.4% (CI95% 12.6 to 20.1%) of the patients relapsed. The Q statistic provided no indications of significant dispersion across studies (Q=32.9, df=27, p=.20), and on the basis of I^2 18.0% of the total variance was related to true heterogeneity between studies. The summary relapse prevalence in the placebo group was 36.4% (CI95% 30.8 to 42.1%). There were no indications of significant dispersion across studies (Q=37.3, df=27, p=.09). Moreover, an I^2 of 27.6% indicated that the heterogeneity between studies was low.

Tolerability, dropouts, and withdrawal symptoms

Data on tolerability and withdrawal symptoms were limited and non-systematic in the studies included, not allowing a meta-analysis. Most studies reported to some extent on adverse events during follow-up and concluded that antidepressants were well tolerated over time. Side effects of antidepressants that were mentioned most often included headache, infections of the upper respiratory tract, influenza-like symptoms, nausea, and insomnia. Dropouts (excluding those for lack of efficacy) were relatively higher in the placebo group than the antidepressant group (summary odds ratio 1.31, CI95% 1.06 to 1.63; n=27 studies) across studies with a follow-up duration ranging from eight to 52 weeks. No significant dispersion was detected (Q=27.1, df=26, p=.40), and I^2 was 4.1% indicating low heterogeneity across studies. Moreover, the summary prevalence of dropout was 21.9% (CI95% 15.3 to 28.5%) in the placebo group and 17.2% (CI95% 13.5 to 20.9%) in the antidepressant group, both across studies with a follow-up duration ranging from eight to 52 weeks. For the summary prevalence of dropout, the Q statistics provided no indications of significant dispersion across studies in either group (antidepressant group Q=32.4, df=26, p=.18; placebo group Q=34.4, df=26, p=.13). Furthermore, I^2 in the placebo group (24.3%) and in the antidepressant group (19.8%) indicated that heterogeneity was low. Higher dropout rates in the placebo group could possibly be due to withdrawal symptoms in the placebo group. However, four studies that specifically reported on withdrawal symptoms stated that there were generally no differences between groups (48,60,70,73), suggesting that adverse effects of antidepressants in the antidepressant group and withdrawal symptoms in the placebo group were balanced. Alternatively, the higher dropout rates in the placebo group might be a masked effect of lack of efficacy. Lack of efficacy can be interpreted as a (partial or beginning) relapse, because all patients were classified as responders before randomisation. If patients who discontinue antidepressants drop out of treatment more often because of lack of efficacy, this would only strengthen our conclusion that those who discontinue antidepressants run a higher risk of relapse.

Discussion

Optimising the long-term prognosis should be an overriding priority when treating patients with anxiety disorders, because relapse and chronicity are common. This meta-analysis examined the risk of relapse when discontinuing antidepressants in patients with anxiety disorder who responded to antidepressant treatment. On the basis of many randomised controlled trials of high quality, we have shown a clear benefit of continuing treatment compared with discontinuation for both relapse (summary odds ratio 3.11, CI95% 2.48 to 3.89; n=28 studies) and time to relapse (summary hazard ratio 3.63, CI95% 2.58 to 5.10; n=11 studies). None of the subgroup analyses or meta-regression analyses reached statistical significance.

Certain aspects of the study population and design may have affected either or both outcomes. Firstly, most studies in this meta-analysis excluded comorbidity to some extent. Given that comorbidity in anxiety disorders is common and associated with chronicity (1), relapse rates in clinical practice are presumably higher. In our subgroup analysis, we found no statistical effect of comorbidity on relapse rates. However, in their randomised controlled trial, Geller and colleagues (59) found that comorbidity primarily increased relapse rates in the placebo group; for example, in the placebo group, the relapse rate was 33% in patients without comorbid disorders and 55% and 77% for those with one or more and two or more disorders, respectively. Geller's findings suggest that the benefits of continuing treatment are greater for patients with comorbidity than for those without comorbidity.

Secondly, summary relapse prevalence was 36.4% (CI95% 30.8 to 42.1%; n=28 studies) in the placebo group compared with 16.4% (CI95% 12.6 to 20.1%, n=28 studies) in the antidepressant group. Duration of follow-up in the individual studies ranged between eight and 52 weeks. Falsely interpreting withdrawal symptoms in the placebo group as relapse would overestimate the protective effect of continuing antidepressants. However, the higher relapse rate in the placebo group is probably attributable to withdrawal symptoms—that is, most of the studies tapered antidepressants thereby diminishing withdrawal symptoms. In addition, ten studies required symptoms to be present on successive visits (24,42,52,59,64–67,72), whereas withdrawal symptoms are transient (74). Also, five studies did post hoc analyses excluding relapses occurring when withdrawal symptoms are most likely (that is, the first seven, 14, or even 28 days after discontinuation) and reported that superiority of antidepressants over placebo remained similar (55,56,58,65,70).

Thirdly, various criteria for response and relapse were used in the individual studies. Using a low threshold to define responders will include patients with residual symptoms in the discontinuation phase, who may run a higher risk for relapse (75), and hence relapse rates may increase.

Fourthly, only relapses of the disorder under study have been included. Given the low stability of anxiety disorders over time (6), the rate of development of 'any disorder' is likely to be substantially higher.

Strengths and weaknesses of study

This meta-analysis summarised the findings of 28 studies, including a total of n=5233 patients. This produces more robust estimates than individual studies. By conducting this meta-analysis, we verified, updated, and extended a previous meta-analysis on this subject (22). We included six additional studies, increasing the total number of patients from n=4121 to n=5233; summarised studies of all anxiety disorders combined; assessed time to relapse as an additional outcome parameter; used a more conservative random effects model; assessed publication bias; did exploratory subgroup analyses and meta-regression analyses; assessed the quality of the included studies; considered dropout rates; and presented adverse events in the follow-up phase. Another strength of our study is that we included only trials with a fixed treatment period. By contrast, observational studies, allowing a flexible duration of the open label phase, are prone to bias favouring continuation of treatment (76).

Drug companies were involved in all except two small studies (64,71). Hence, we should be aware of the probability of both publication bias and sponsorship bias (77). To limit potential bias, we thoroughly searched for non-published studies and included these if sufficient information was available. We found six unpublished studies, four with negative results, one with positive results, and one with unknown results, thereby suggesting publication bias. Two of these could not be included due to a lack of information. One showed a non-significant trend favouring continuation treatment (47); inclusion of this study in the meta-analysis might have slightly attenuated the summary odds ratio. The potential effect on the summary odds ratio of the second study is unknown, as the necessary data are unavailable (49). Four of the unpublished studies provided sufficient information and could be included in the meta-analysis (50–53). Three of these unpublished studies found no significant effect of continuation treatment, and one found a positive effect of continuation treatment. Including these unpublished studies has resulted in a lower odds ratio compared with excluding (the four) unpublished studies (for example, excluding unpublished studies, odds ratio=3.38, CI95% 2.76 to 4.12; including unpublished studies, odds ratio=3.11, CI95% 2.50 to 3.86).

To further assess potential biases, we examined whether selective reporting was present in individual studies. We found several indications of selective reporting. In four articles, the abstract was incomplete (42,62,69,71). In addition, one study had planned to analyse time to relapse with a Cochran- Mantel-Haenzel test but did not report test results (48), and three studies reported the hazard ratio for time to relapse but gave incomplete information about the 95% confidence interval (24,54,58). Irrespective of whether these shortcomings are related to the involvement of drug companies, it seems unlikely that they change our conclusion for the following reasons: we most likely included most unpublished studies in the meta-analysis; adjusting odds ratios attenuated the strength of

the association, but the protective effect of continuing antidepressants remained substantial; missing confidence intervals were estimated and included in meta-analysis; and a meta-regression on the quality of studies (including the aspect of selective reporting) was not statistically significant.

We did subgroup analyses, which showed no statistical significant differences. Findings of subgroup analyses should, however, be interpreted cautiously, because statistical power to detect genuine differences is limited. Moreover, these are observational comparisons; studies included in the subgroup analysis may differ in other aspects too. Only direct comparisons can verify whether risk of relapse might be related to type of anxiety disorder, type of antidepressant, mode of discontinuation, duration of treatment and follow-up, comorbidity, and allowance of concurrent psychotherapy. In addition, a network meta-analysis is worth considering to extend the meta-regression analyses.

Moreover, the reported summary relapse prevalences per treatment group should be interpreted with caution because individual studies differ with regard to their follow-up duration, ranging from eight to 52 weeks. A final limitation is that the maximum duration of treatment was limited to 52 weeks. Randomised studies with a longer duration do not exist. Up until one year, we found a clear advantage of continuing antidepressants. However, on the basis of our meta-analysis, we cannot determine whether a relatively 'safe' period exists after 52 weeks of treatment when antidepressants can be discontinued without the associated risk of relapse.

Clinical implications and guideline recommendations

Altogether our results imply that, for a treatment duration of up to one year, antidepressants outperform placebo in preventing relapse and are well tolerated over time. Additionally, antidepressants seem to be superior to placebo in terms of quality of life (23), and direct medical costs associated with relapse might offset the costs of antidepressants (78). Although most guidelines recommend one year of follow-up, some advice shorter periods for specific anxiety disorders (for example, panic disorder (14,79)); these recommendations may need reconsideration.

We have no definite answer as to whether discontinuing antidepressants earlier—that is, within a year—is unwise. Our exploratory meta-regression analysis assessing the effect of duration of treatment was statistically non-significant. In line with this, time to restarting an antidepressant was found to be similar in patients who discontinued antidepressants within six months and those who continued antidepressants for six to 12 months (80).

Likewise, as studies included in this meta-analysis had a treatment duration up to one year, we have no answer as to whether patients should continue or may safely discontinue their antidepressants after this period. On the one hand, we can hypothesise that with longer durations of treatment, improvement continues and functioning improves, thereby drifting further away from a relapse. On the other hand, in a study with a naturalistic design, relapse rates after discontinuation were high, even after three years

of sustained remission on treatment (26). Given the importance of this for daily clinical care, randomised controlled trials with long treatment durations are needed in patients who responded to antidepressants. These studies should directly compare various durations of treatment. To date, such studies have been done by Rickels and colleagues and by Mavissakalian and Perel (24,28). Both studies had small sample sizes, and, additionally, in part of the sample of Mavissakalian and Perel, discontinuation was not blinded. Results were contradictory. Rickels and colleagues found significantly higher relapse rates following discontinuation in patients treated for six months (53.7%) than in those patients treated for 12 months (32.4%) (24). In contrast, Mavissakalian and Perel found similar relapse rates in patients who were treated for six months and in those who were treated for 12-30 months before discontinuation (28). Until more data become available, no rational advice can be provided to patients to optimise their long-term prognosis after this period of one year. We emphasise that the guidelines' advice to continue treatment for a year should not be interpreted as advice to taper drugs after this period. Thus, by suggesting tapering of drugs following sustained remission, current guidelines are too optimistic. Unfortunately, the discussion as to whether discontinuing antidepressants is wise often does not take place between doctors and their patients (81).

As described above, continuing antidepressants decreases the risk of relapse and thereby improves the long-term prognosis. However, when 36.4% of the patients relapse, 63.6% do not. In other words, most patients do well when discontinuing treatment. Furthermore, relapse may also occur during continuation of antidepressants (16.4%). In addition to relapse, patients' preferences and adverse effects should be taken into account when deciding whether to continue or discontinue antidepressants. Some patients have an aversion to antidepressants or view long-term use as problematic (82,83). According to clinical experience, patients find side effects more difficult to accept in a remitted state than in the acute phase of their disorder. Moreover, research conducted among patients in primary care who use antidepressants predominantly because of anxiety or depressive disorders has shown the importance of side effects for patients; for a substantial minority, the efficacy of antidepressants does not outweigh the side effects (82). Doctors should inform patients about the risk of relapse and decide collaboratively with the patient whether the benefits of discontinuation are worth the risk of relapse in their specific case.

To improve knowledge about the advantages and disadvantages of antidepressant discontinuation, some important research questions need to be answered. Firstly, there are indications that for some patients, drug treatment is less effective when reinstated after relapse. This is important because relapse could then turn into chronicity. Secondly, whether specific psychological interventions may decrease relapse after discontinuation is unknown. Lastly, insight into predictors of relapse may enable a personal risk estimate.

Conclusions

Anxiety disorders often run a chronic course, so long-term considerations should direct treatment. In the acute phase, both cognitive behavioural therapy and antidepressants can be considered. When considering antidepressants in acute phase treatment, the relapse risk in the case of later discontinuation needs to be discussed and evaluated from the start of the treatment. On the basis of the evidence presented here, the advice is to continue antidepressants for at least a year. After this period, no evidence-based advice can be provided. The lack of evidence after this period should not be interpreted as explicit advice to discontinue antidepressants after one year. Guidelines that suggest tapering antidepressants following sustained remission should be reworded. When deciding to continue or discontinue antidepressants in individual patients, the relapse risk should be considered in relation to side effects and the patient's preferences. Patients and their doctors need to exchange views on what seems best for the individual patient in the long-term.

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Appendix 5.1: Search strategy PubMed

Search (((((("Anxiety Disorders"[Mesh] OR anxiety disorder* [tiab] OR generalized anxiety disorder* [tiab] OR generalised anxiety disorder* [tiab] OR agoraphobi* [tiab] OR panic* [tiab] OR phobi* [tiab] OR obsessive-compulsive [tiab] OR post-traumatic* [tiab] OR posttraumatic* [tiab] OR traumatic* [tiab] OR anxiety disorder* [OT] OR generalized anxiety disorder* [OT] OR generalised anxiety disorder* [OT] OR agoraphobi* [OT] OR phobi* [OT] OR obsessive-compulsive [OT] OR post-traumatic* [OT] OR posttraumatic* [OT] OR traumatic* [OT])) AND ("Antidepressive Agents" [Pharmacological Action] OR "Antidepressive Agents"[Mesh] OR "Serotonin Uptake Inhibitors"[Mesh] OR antidepressiv* [tiab] OR antidepressant* [tiab] OR SSRI* [tiab] OR SNRI* [tiab] OR TCA* [tiab] OR serotonin reuptake inhibitor* [tiab] OR antidepressiv* [OT] OR antidepressant* [OT] OR serotonin reuptake inhibitor* [OT] OR SSRI* [OT] OR SNRI* [OT] OR TCA* [OT])) AND ("Secondary Prevention"[Mesh] OR "Recurrence"[Mesh] OR continuation* [tiab] OR continuing [tiab] OR discontinuation* [tiab] OR discontinuing [tiab] OR relaps* [tiab] OR remission [tiab] OR recurren* [tiab] OR maintenance [tiab] OR withdrawal [tiab] OR continuation* [OT] OR continuing [OT] OR relaps* [OT] OR remission [OT] OR recurren* [OT] OR maintenance [OT] OR withdrawal [OT]))) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo* [tiab] OR randomly[tiab] OR RCT[tiab] OR controlled trial* [tiab] OR clinical trial* [tiab] OR randomized[OT] OR placebo* [OT] OR randomly[OT] OR RCT [OT] OR controlled trial* [OT] OR clinical trial* [OT])

This search strategy has been translated for additional searches in both Embase and Cochrane.

Appendix 5.2: Quality assessment

Quality assessment per study according to Cochrane Tool for assessing risk of bias (32).

	Selection bias		Performance bias		Detection bias	Attrition bias	Reporting bias	# scoring high
Reference	Random sequence generation	Allocation concealment	Blinding of patients	Blinding of providers	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	
(55)	Low	Low	Low	Low	Low	High	Low	1
(56)	Low	Low	High	Low	Low	High	Low	2
(68)	Low	Low	Low	Low	Low	High	Unclear	1
(41)	Low	Unclear	Low	Low	Low	Low	Unclear	0
(48)	Unclear	Unclear	High	Low	Low	Low	Low	1
(65)	Unclear	Unclear	Low	Low	Low	High	Unclear	1
(58)	Low	Low	Low	Low	Low	Low	High	1
(59)	Unclear	Unclear	High	Low	Low	High	Low	2
(50)	Unclear	Unclear	High	Low	Low	High	High	3
(51)	Unclear	Unclear	High	Low	Low	High	High	3
(52)	Unclear	Unclear	Low	Low	Low	High	High	2
(53)	Unclear	Unclear	Low	Low	Low	High	High	2
(60)	Low	Low	High	Low	Low	High	Unclear	2
(67)	Unclear	Unclear	High	Low	Low	Low	Unclear	1
(61)	Unclear	Low	Low	Low	Low	High	High	2
(62)	Unclear	Low	Low	Low	Low	High	Low	1
(69)	Unclear	Unclear	Low	Low	Low	Low	High	1
(64)	Low	Low	Low	Low	Low	High	Low	1
(42)	Unclear	Unclear	Low	Low	Low	High	High	2
(70)	Low	Low	High	Low	Low	Low	Low	1
(66)	Unclear	Unclear	High	Low	Low	High	Low	2
(24)	Unclear	Unclear	Low	Low	Low	High	High	2
(63)	Unclear	Unclear	Low	Low	Low	High	Low	1
(71)	Low	Low	Low	Low	Low	Unclear	Low	0
(72)	Unclear	Low	Low	Low	Low	High	High	2
(57)	Low	Low	Low	Low	Low	High	Low	1
(54)	Low	Unclear	Low	Low	Low	Low	High	1
(73)	Unclear	Unclear	High	Low	Low	Low	Low	1

Appendix 5.3: Characteristics of included studies

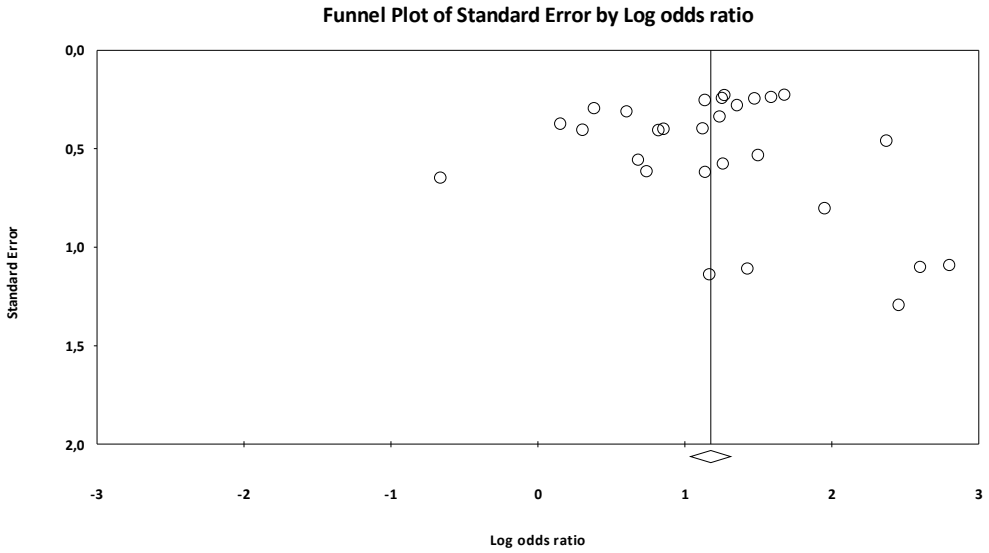
Characteristics of included studies.

Ref	Anxiety disorder	Age[a]		Antidepressant	Dose mg/day	Discontinuation [b]	Duration treatment before randomisation in weeks	Duration follow-up in weeks
		Antidep.	Placebo					
(55)	GAD	41 (18-65)*	42 (18-64)*	Escitalopram	20	Taper	12	24[c]
(56)	GAD	43.3 (13.3)		Vortioxetine	5-10	Abrupt	20	24[d]
(68)	PTSD	44.9 (9.8)	42.0 (10.8)	Sertraline	50-200	Abrupt	24	28
(41)	PTSD	44.0 (12.0)	44.1 (11.7)	Fluoxetine	20-60	Taper	24	26
(48)	GAD	45.0 (13.2)	45.7 (14.1)	Duloxetine	60-120	Taper	26	26
(65)	PD	37.3 (10.9)	39.5 (10.7)	Venlafaxine	75-225	Taper	12	26
(58)	OCD	35.4 (12.4)	35.8 (11.1)	Escitalopram	10 or 20	Taper	16	24
(59)	OCD	11.8 (2.56)	11.6 (2.88)	Paroxetine	10-60	Abrupt	16	16
(50)	OCD	40.7 (10.5)	41.1 (12.5)	Paroxetine	20-60	Abrupt	26	26
(51)	PD	Par10: 37.8 (12.9) Par20: 34.4 (11.0) Par40: 35.3 (10.5)	39.2 (10.1)	Paroxetine	10; 20; or 40	Abrupt	22	12
(52)	SP	37.2 (11.9)	32.5 (10.5)	Paroxetine	20-50	Taper	24	16
(53)	PTSD	42.7 (13.9)	42.8 (12.0)	Paroxetine	20-50	Taper	12	16
(60)	OCD	45.1 (11.7)	40.1 (13.0)	Paroxetine	20-60	Abrupt	26	26
(67)	PD	35.3 (8.1)	36.1 (9.5)	Sertraline	25-100	Abrupt	8	8
(61)	OCD	39.2 (11.5)	39.5 (10.8)	Sertraline	50-200	Taper	52	28
(62)	OCD	34.5 (10.24)		Mirtazapine	30-60	Taper	12	8
(69)	PTSD	37.1 (9.4)	39.4 (9.4)	Fluoxetine	20-80	Taper	12	24
(64)	PD	34.28 (8.23)	37.89 (9.92)	Imipramine	10-75	Taper	24	52
(42)	PD	38.7 (9.5)	36.4 (11.1)	Fluoxetine	10 or 20	Taper	10	24
(70)	SP	36 (18-78)*	38 (19-68)*	Escitalopram	10 or 20	Abrupt	12	24
(66)	PD	41.0 (10.8)	40.3 (11.4)	Sertraline	50-200	Abrupt	52	28
(24)	GAD	49.8 (15.8)		Venlafaxine	75-225	Taper	26	26
(63)	OCD	39.5 (11.3)	42.2 (14.7)	Fluoxetine	20-60	Taper	20	52
(71)	SP	Not reported		Paroxetine	20-50	Taper	11	12
(72)	SP	38.1 (11.7)	38.2 (11.2)	Paroxetine	20-50	Taper	12	24
(57)	GAD	45.9 (14.0)	47.0 (15.1)	Agomelatine	25-50	Abrupt	16	26
(54)	GAD	43.0 (12.7)	43.7 (13.1)	Paroxetine	20-50	Taper	8	24
(73)	SP	37.24 (24-57)*	35.06 (21-46)*	Sertraline	50-200	Abrupt	20	24

[a]Studies with an '*' report mean age and age range, all other studies report mean age and standard deviation. [b]Fluoxetine was discontinued abruptly in all studies, however given the relatively long half-life time of fluoxetine, this medication is considered to taper itself. [c](55) had a minimum follow-up duration of 24 weeks, and depending on when a participant was included, a maximum follow-up of 76 weeks. [d](56) had a minimum follow-up duration of 24 weeks, and depending on when a participant was included, a maximum follow-up of 56 weeks.

N treatment	N follow-up		N relapse during follow-up		Concurrent psychotherapy allowed	Comorbidity mostly excluded	Role pharmaceutical companies
	Antidep.	Placebo	Antidep.	Placebo			
491	187	188	34	98	Yes	Yes	Yes, funded/supported/sponsored by
687	224	227	26	66	No	Yes	Yes, author(s) salary paid by
380	38	46	6	21	No	No	Yes, funded/supported/sponsored by
123	30	32	6	15	Yes	No	Yes, medication provided by
887	216	213	28	84	Yes	Yes	Yes, funded/supported/sponsored by
313	89	80	20	40	No	Yes	Yes, funded/supported/sponsored by
468	163	157	38	81	No	Yes	Yes, author(s) salary paid by
335	95	98	33	43	No	No	Yes, funded/supported/sponsored by
154	20	24	8	14	No	Yes	Yes, funded/supported/sponsored by
278	43	43	2	11	Yes	Yes	Yes, funded/supported/sponsored by
98	27	28	8	5	Yes	Yes	Yes, funded/supported/sponsored by
265	87	86	17	19	No	Yes	Yes, funded/supported/sponsored by
263	53	51	20	30	No	No	Yes, funded/supported/sponsored by
394	119	121	12	16	Yes	Yes	Yes, funded/supported/sponsored by
649	109	114	10	27	No	Yes	Yes, funded/supported/sponsored by
30	7	8	2	5	No	Yes	Yes, funded/supported/sponsored by
226	69	62	4	10	No	Yes	Yes, funded/supported/sponsored by
110	29	27	1	10	Yes	No	No
165	38	50	1	4	Yes	No	Yes, funded/supported/sponsored by
517	190	181	42	91	No	Yes	Yes, funded/supported/sponsored by
398	92	89	11	21	Yes	No	Yes, funded/supported/sponsored by
268	82	54	8	29	Yes	Yes	Yes, medication provided by
130	36	34	7	11	No	No	Yes, funded/supported/sponsored by
36	8	8	1	5	Yes	No	No
437	162	161	22	61	Yes	Yes	Yes, funded/supported/sponsored by
477	113	114	22	35	No	Yes	Yes, funded/supported/sponsored by
652	274	287	30	115	Yes	Yes	Yes, funded/supported/sponsored by
Unclear	25	25	1	9	No	No	Yes, funded/supported/sponsored by

Appendix 5.4: Funnel plot proportion of relapse



Appendix 5.5: Funnel plot time to relapse